NLRP3 Inflammasome-Related Proteins Are Upregulated in the Putamen of Patients With Multiple System Atrophy(Abstract_要旨)

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論文題目	NLRP3 Inflammasome-Related Proteins Are Upregulated in the Putamen of Patients With Multiple System Atrophy （多系統萎縮症の被殻におけるNLRP3インフラマソームの免疫組織学的検討）		

（論文内容の要旨）

Multiple system atrophy (MSA) is a progressive neurodegenerative disorder characterized by parkinsonism, ataxia, and autonomic dysfunction. There is currently no specific treatment for MSA. Reasons for dopaminergic therapy failure in MSA are attributed to degeneration of postsynaptic neurons in the putamen, projective fiber loss from the nigra to putamen, and neuronal loss in the substantia nigra. To overcome these problems, the pathomechanism of degeneration in the putamen of MSA patients requires elucidation.

In the putamina of MSA patients, there are glial cytoplasmic inclusions (GCIs), neuronal loss, microglial infiltration, and gliosis. GCIs are the hallmark of MSA pathology and its major component is α-synuclein in oligodendrocytes. Additionally, aggregated α-synuclein has been implicated in prompting microglia-mediated inflammation in MSA in both disease initiation and progression. These pathological features imply that regulation of microglial activation may be a therapeutic target for MSA. However, the precise relationship between α-synuclein aggregation and microglial activation has not been elucidated.

Recently, the inflammasome has been reported to link aggregation of pathogenic proteins and microglial activation in a variety of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). In particular, the nucleotide-binding domain, leucine-rich repeats-containing family, pyrin domain-containing-3 (NLRP3)-related inflammasome is related to the neurodegenerative processes of abnormal protein accumulation. These abnormal proteins, including ß-amyloid and α-synuclein, stimulate invasive microglia. The NLRP3 inflammasome complex consists of NLRP3, apoptotic speck protein containing a caspase recruitment domain (ASC) and cysteine aspartic acid protease 1 (Caspase 1). Various signals through the Toll-like receptor/nuclear factor-κB (TLR/NF-κB) pathway recruit NLRP3 inflammasome-related proteins into the NLRP3 inflammasome complex, leading to the transcription of pro-IL-1ß and pro-IL-18. This results in the generation of mature cytokines IL-1ß and IL-18. Regulation of the NLRP3 inflammasome may alleviate neuroinflammation and neurodegenerative processes in AD and PD models. However, the understanding of inflammasome activation and its relationship with GCIs, microglial infiltration, and gliosis in MSA patients is limited.

This study reports the relationship between NLRP3 inflammasome-related proteins and microglial activation in the putamen of MSA patients. Single-labeling immunohistochemistry staining of the posterior putamen in post-mortem brains from 11 cases of MSA, five of PD, and six age-matched controls (CTL) were assessed. In MSA cases, this study found that the density of microglia expressing NLRP3 inflammasome-related proteins was increased and was significantly related to the deposition of phosphorylated α-synuclein (p-Syn)-positive glial cytoplasmic inclusions, tyrosine hydroxylase (TH)-positive fiber loss, and gliosis of glial fibrillary acidic protein-positive astrocytes. Moreover, the ratio of cells expressing NLRP3 inflammasome-related proteins tended to increase in the microglia of MSA patients. Morphologically, these immunopositive microglia had relatively large, round cell bodies which were compatible with rounded amoeboid microglia. Double-labeling immunofluorescence staining confirmed colocalization of NLRP3 inflammasome-related proteins and Cluster of Differentiation 68 (CD68) in MSA.

These pathological results indicate that the NLRP3 inflammasome plays a crucial role in microglial activation and infiltration in MSA. The findings suggest that microglial activation and IL-1ß pathway activation can be attributed to aggregated α-synuclein, and also associated with neuronal loss and gliosis in the putamen of MSA patients, as neuronal injury and degeneration activate astrocytes and induce gliosis. The degree of microglial infiltration and upregulation of inflammasome-related proteins were also related to TH-positive fiber loss.

This study proposes that abnormal α-synuclein activates microglial NLRP3 inflammasome leading to IL-1ß release, microglial infiltration, gliosis, axonal damage, and neuronal death in MSA. Thus, regulation of microglial NLRP3-inflammasome activation could be a potential therapeutic target for neuronal survival and degeneration in MSA.

（論文審査の結果の要旨）

NLRP3インフラマソームは、炎症性サイトカインであるインターロイキン1β産生を制御する細胞内の蛋白質複合体である。NLRP3インフラマソームが、アルツハイマー病、パーキンソン病（PD）などの神経変性疾患の発症や進行と関わっていることは報告されているが、多系統萎縮症（MSA）における関与については不明な点が多い。

申請者らはMSA、PD、およびコントロール剖検脳を用いて、NLRP3インフラマソーム関連タンパクの発現変化について、神経病理学的解析を行った。また、α-シヌクレイン（α-syn）陽性封入体、ドーパミン作動性神経線維やグリア細胞の動態との関連についても検討した。その結果、MSAでは、PDやコントロールと比較して、被殻後部外側部にNLRP3インフラマソーム関連タンパク質陽性ミクログリアが多く認められた。相関解析では、NLRP3インフラマソーム関連タンパク陽性細胞の増加とα-syn陽性グリア細胞質内封入体、ドーパミン作動性神経細胞脱落、アストロサイト活性化の程度が相関することが示された。これらの結果から、NLRP3インフラマソームが、MSAの病態に関与することが示唆された。

以上の研究はMSAにおけるNLRP3インフラマソームの役割の一端を明らかにし、MSAの分子病態解明に寄与するところが多い。

したがって、本論文は博士（医学）の学位論文として価値あるものと認める。

なお、本学位授与申請者は、平成３１年１月４日実施の論文内容とそれに関連した試問を受け、合格と認められたものである。

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